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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,622	11/18/2003	Xian-Ping Lu	4865-105 US	4873

7590 03/17/2006

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EXAMINER	
COLEMAN, BRENDA LIBBY	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 03/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,622	LU ET AL.	
	Examiner	Art Unit	
	Brenda L. Coleman	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 8-23* is/are rejected.

7)☒ Claim(s) *6 and 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-28 are pending in the application.

Election/Restrictions

1. Applicant's election of Group I in the reply filed on January 17, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 24-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on January 17, 2006.

Specification

3. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In evaluating the enablement question, several factors are to be considered. In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988); Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

HOW TO USE: Claims 17-19 are to a method of treating a disease, which is associated with Peroxisome Proliferator-Activated Receptors (PPAR). Any evidence presented must be commensurate in scope with the claims and must clearly demonstrate the effectiveness of the claimed compounds. The scope of the method claims are not adequately enabled solely based on inhibition of nuclear receptors provided in the specification. Diseases and/or disorder(s) known to be associated with (PPAR) include insulin resistance and hyperglycemia in type II diabetes. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims. It is difficult to treat many of the disorders claimed herein. Instant claim language embraces disorders not only for treatment but for **prevention** which is not remotely enabled. It is presumed in the prevention of the diseases and/or disorders claimed herein there is a way of identifying those people who may develop diabetes, cardiovascular disease, etc. There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disorders claimed herein.

In general, pharmacological activity is a very unpredictable area. In cases involving physiological activity "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). Since this case involves unpredictable in-vivo physiological activities, the scope of the enablement given in the disclosure presented here was found to be low.

The specification has only one working example on the use of the substituted tricyclic ring systems. There must be evidence to justify the contention that the claimed compounds can be useful in the treatment of "type I diabetes, type II diabetes, dyslipidemia, syndrome X, cardiovascular disease, atherosclerosis, hypercholesteremia, and obesity".

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

5. Claims 1-5 and 8-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

a) Claims 1-3 and 8-23 are vague and indefinite in that it is not known what is meant by alkenynyl in the definition of substituents on ring A and ring B.

b) Claims 1, 3 and 8-23 are vague and indefinite in that it is not known what is meant by alkenynyl in the definition of R^6, R^1, R^2, R^3, R^4, R^5 and the substituents of R^4 and R^5, when R^4 and R^5 together form a 5 or 6 membered ring.

c) Claims 1, 8 and 17-23 are vague and indefinite in that it is not known what is meant by the period, which appears at the end of the definition of Ar^1 indicating the end of the claim which is not so.

d) Claims 4 and 5 are vague and indefinite in that it is not known what is meant by the semi-colon, which appears at the end of each claim.

e) Claims 8 and 9 are vague and indefinite in that it is not known what is meant by C1-6alkyl and C1-6alkoxyl in the definition of the substituents on the Ar^1 ring.

f) Claims 8 and 9 are vague and indefinite in that it is not known what is meant by C1-6alkyl and C1-6alkoxyl in the definition of the substituents on the Ar^2 ring.

g) Claims 8 and 9 are vague and indefinite in that it is not known what is meant by arylene or a divalent heterocyclic group in the definition of Ar^2, where Ar^2 is not a divalent moiety.

h) Claims 8 and 9 are vague and indefinite in that it is not known what is meant by non C1-6alkyl and C1-6alkoxyl in the definition of the substituents on the Ar^2 ring.

i) Claims 10 and 11 are substantial duplicates of claim 1 as the only difference is a statement of intended use, which is not given material weight. Note In re Tuominen 213 USPQ 89.

j) Claims 10-19 are vague and indefinite in that the claim provides for the use of claimed compounds, but the claim does not set forth any steps involved in determining which are the diseases capable of being mediated by nuclear receptors or Peroxisome Proliferator-Activated Receptors. Determining whether a given disease responds or does not respond to such an inhibitor will involve undue experimentation. Suppose that a given drug, which has inhibitor properties in vitro, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment? Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus iv or in a time release po formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active in vitro, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many different structurally related inhibitors must be tried before one concludes that a specific compound does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of which are inhibitors in vitro, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property, which the second drug is capable. It is common for a

drug, particularly in diabetes and cardiovascular disease, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to affect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some totally different drug. There are for example, agents in antiviral and anticancer chemotherapy, which are not themselves effective, but are effective treatments when the agents are combined with something else.

Consequently, determining the true scope of the claim will involve extensive and potentially inconclusive research. Without it, one skilled in the art cannot determine the actual scope of the claim. Hence, the claim is indefinite.

k) Claim 13 recites the limitation "nuclear receptors" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

l) Claim 15 is vague and indefinite in that it does not end with a period.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1, 3, 5 and 10-23 are rejected under 35 U.S.C. 102(e) as being anticipated by Jeppesen et al., U.S. Patent Application Publication 2003/0055076. Jeppesen teaches the compounds, compositions and method of use of the compounds of formula I where ring A and ring B are benzene rings; X is a valence bond; R^1 is H; R^2 is H or CH_3; R^3 is H; R^4 and R^5 together form an benzene ring; Alk^1 is $-CH_2CH_2-$; Alk^2 is $-CH_2-$; Ar^1 is benzene and Ar^2 is a benzene ring. See examples 7 and 8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3, 5 and 10-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jeppesen et al., U.S. Patent Application Publication 2003/0055076. The generic structure of Jeppesen encompasses the instantly claimed compounds (see Formula (I) on page 3) and for the same uses as claimed herein. Examples 7 and 8, which anticipates the compounds of the instant invention differ only in the substituents A, a, R^1, R^2, R^3, R^4 and R^5. Page 3, paragraphs [0042] through [0049] defines the

substituents A, a, R^1, R^2, R^3, R^4 and R^5 as follows: A is a fused tricyclic ring system optionally substituted with one or more substituents selected from halogen, hydroxyl, cyano, amino, C_{1-6}-alkylamino, C_{3-6}-cycloalkylamino, C_{1-6}-dialkylamino or carboxy; or C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{2-4}-alkenyl, C_{2-6}-alkynyl, C_{1-6}-alkoxy, C_{3-6}-cycloalkoxy, C_{1-6}-alkylthio, C_{3-6}-cycloalkylthio each of which is optionally substituted with halogen; aryl, aryloxy, arylthio, acyl, aralkyl, aralkoxy, heteroaryl, heteroaralkyl, heteroaryloxy, heteroaralkoxy each of which is optionally substituted with halogen, perhalomethyl or perhalomethoxy; a is 1, 2, or 3; R^1 and R^2 are independently hydrogen, halogen, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, C_{1-6}-alkoxy or C_{3-6}-cycloalkoxy; R^3 and R^4 are independently hydrogen or halogen; and R^5 is hydrogen, C_{1-6}-alkyl or C_{3-6}-cycloalkyl. The compounds of the instant invention are generically embraced by Huff in view of the interchangeability of the substitutions of the carbazole ring. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to select for example ethoxy or isopropyl as well as other possibilities from the generically disclosed alternatives of the reference and in so doing obtain the instant compounds in view of the equivalency teachings outlined above.

Claim Objections

8. Claims 6 and 7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. None of the prior art of record or a search in the pertinent art area teaches the compounds as claimed herein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda L. Coleman whose telephone number is 571-272-0665. The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brenda Coleman

Brenda L. Coleman
Primary Examiner Art Unit 1624
March 14, 2006